

# Immunological and Genetic Markers Predicting Treatment Outcome in Hepatitis C Virus Infection

## Akademisk avhandling

som för avläggande av medicine doktorexamen vid avdelningen för infektionssjukdomar, Göteborgs universitet, kommer att försvaras i föreläsningssalen, Guldhedsgatan 10A, Göteborg

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av

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Avhandlingen baseras på följande delarbeten:

- I. Askarieh G, Alsio A, Pugnale P, Negro F, Ferrari C, Neumann AU, Pawlotsky JM, Schalm SW, Zeuzem S, Norkrans G, Westin J, Söderholm J, Hellstrand K, Lagging M. Systemic and intrahepatic interferon- $\gamma$ -inducible protein 10 kDa predicts the first-phase decline in hepatitis C virus RNA and overall viral response to therapy in chronic hepatitis C. *Hepatology* 2010, 51: 1523-30.
- II. Falconer K, Askarieh G, Weis N, Hellstrand K, Alaeus A, Lagging M. IP-10 predicts the first phase decline of HCV RNA and overall viral response to therapy in patients co-infected with chronic hepatitis C virus infection and HIV. *Scand J Infect Dis* 2010, 42: 896-901.
- III. Lagging M, Askarieh G, Negro F, Bibert S, Söderholm J, Westin J, Lindh M, Romero A, Missale G, Ferrari C, Neumann AU, Pawlotsky JM, Haagmans BL, Zeuzem S, Bochud PY, Hellstrand K. Response prediction in chronic hepatitis C by assessment of IP-10 and *IL28B*-related single nucleotide polymorphisms. *PLoS One* 2011. *In press*.
- IV. Askarieh G, Lagging M, Lindh M, Norkrans G, Wejstål R, Westin J, Hellstrand K, and Söderholm J. Specific CD26 activity predicts treatment efficacy in chronic hepatitis C. *In manuscript*.



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## ABSTRACT

Hepatitis C is a blood-borne infection caused by the hepatitis C virus (HCV). A chronic infection, which develops in most infected subjects, may lead to liver cirrhosis with ensuing liver dysfunction and liver cancer. The current standard therapy in chronic hepatitis C is a combination of pegylated interferon- $\alpha$  (peg-IFN) and ribavirin (RBV) for 24-48 weeks. Eradication of HCV (*i.e.* sustained virological response, SVR) is achieved in 50-80% of patients, albeit with significant side-effects. Further understanding of host factors that determine the effectiveness of treatment may provide diagnostic tools to distinguish patients who will be cured from those in whom treatment is likely to be futile.

The aim of this thesis was to identify biomarkers to predict outcome of combination therapy in chronic HCV infection. The biomarkers studied included IP-10, soluble CD26 (sCD26), and single nucleotide polymorphisms (SNPs) in proximity of genes encoding cytokines of the IFN- $\lambda$  family.

Interferon- $\gamma$ -inducible protein 10 kDa (IP-10 or CXCL10) is a chemokine that attracts mononuclear blood cells to sites of infection. IP-10 is produced by several cell types, including hepatocytes, and blood levels of IP-10 at onset of therapy are reportedly elevated in patients infected with HCV genotypes 1 or 4 who do not achieve SVR. In the studies included in this thesis, it was observed that IP-10 in plasma is mirrored by intrahepatic IP-10 mRNA expression, and strongly predicts the reduction of HCV RNA in blood already during the first days of peg-IFN/RBV therapy for all HCV genotypes. Additionally, it was observed that a combined assessment of systemic IP-10 and *IL28B*-related SNPs further enhances the prediction of early viral decline and the final treatment outcome among HCV genotype 1-infected patients.

Serum dipeptidyl peptidase IV, also known as CD26, cleaves a dipeptide from the N-terminal region of IP-10, generating a truncated, competitive antagonist form of IP-10. Recent reports demonstrated that serum IP-10 in HCV patients is dominated by truncated IP-10. In this setting, the specific sCD26 activity was found to predict the effectiveness of peg-IFN/RBV therapy in chronic hepatitis C, and enhance the value of established outcome predictors.

**Keywords:** IP-10, CXCL10, CD26, hepatitis C virus, interferon, ribavirin, treatment, *IL28B*  
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